PP#4258

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

APR 24 1995

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Subject: PP#3F4258, PP#1F3973/1H5611 Abamectin in or on bell peppers. Registrant's response to CBTS review (6/21/94) and additional bell pepper residue data. CBTS# 14207; DP Barcode D206550; MRID#433346-00: MRID#42949801, Fax 4/19/95.

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THROUGH: Robert Quick, Section Head
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Merck & Co., Inc. requests the establishment of permanent tolerances for the combined residues of the insecticide avermectin B_1 (also referred to as abamectin) and its delta-8,9 isomer on the raw agricultural commodities bell peppers and tomatoes at 0.01 ppm. A crop group tolerance is not being proposed due to a lack of residue data on small pepper varieties. This submission is in two parts. The first is in response to the CBTS review of 6/21/94. Original CBTS deficiencies, Merck's response, and CBTS responses are in the appropriate discussion section. The second is additional residue data of avermectin in/on bell peppers.

Even though the Section F proposes a tolerance on tomatoes, permanent tolerances for the combined residues of the insecticide/miticide avermectin B_1 and its delta-8,9-isomer have already been established for tomatoes at 0.01 ppm (40 CFR §180.449) and tomato pomace at 0.07 ppm (40 CFR §186.300). Avermectin B_1 is comprised of ≥80% avermectin B_1a and ≤20% avermectin B_1b. Avermectin B_1a is 5-O-demethyl avermectin A_1a; Avermectin B_1b is 5-O-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl) avermectin A_1a.

Abamectin.026

A Reregistration Standard has not been prepared for avermectin.

CONCLUSIONS

1. The product chemistry of technical grade avermectin has been adequately described. No further data is required for this proposed use.

2. The proposed use directions in Section B are adequate. No further data are required for this proposed use.

3. The metabolism of avermectin in/on fruiting vegetables is understood. No further data is required for this proposed use. The residues of concern are avermectin B_1 and the delta-8,9-isomer.

4. The metabolism of avermectin in animals is adequately understood to support this use on bell peppers. The residues of concern in animals are avermectin B_1 and the delta-8,9-isomer.

5. Adequate enforcement methods are available for avermectin B_1 and the delta-8,9-isomer. No further methodology is necessary for this proposed use.

6. Avermectin B_1a, avermectin B_1b and the delta-8,9-isomer are not recovered by published multiresidue methods. No further data concerning multi residue methodology is necessary for this proposed use.

7a. There are sufficient residue data in the petition to support the proposed tolerance on bell peppers. Residues of avermectin B_1 and the delta-8,9-isomer resulting from the proposed use are not expected to exceed the proposed 0.01 ppm tolerance. No additional residue data are required for bell peppers.

7b. The studies submitted here fall under the scope of the GLPs in 40 CFR §160.

7c. The geographic diversity of the studies presented on bell peppers are adequate to represent the growing environment throughout the United States. No further data are required for the proposed use on bell peppers.

8. There were no storage stability data presented with this amendment. There are sufficient storage stability data on related crops to support the field trial residue data for bell peppers.

9. There are no known animal feed stock uses for bell peppers. Consequently, secondary residues in meat, milk, poultry, and eggs are not expected to be a problem. In addition, the petitioner has submitted for reference a copy of a revised Section F for PP#1F3973/1H5611 proposing the 0.015 ppm tolerance on fat, cattle.

This tolerance in fat has not yet been established. The fat tolerance should be established to cover secondary residues resulting from presently registered uses on other crops.

10. Analytical standard materials for avermectin B_1 and the delta-8,9-isomer are available.

11. Codex has established tolerances in/on tomatoes and fruiting vegetables of 0.02 ppm. For compatibility purposes the proposed tolerance would therefore need to be increased to 0.02 ppm. The tolerance expression would not need to be changed. The increase for the purposes of harmonization would need to be based on toxicological considerations.

12. Residue levels for acute and chronic dietary risk exposure assessment for bell peppers are 0.01 and 0.002 ppm respectively.

Recommendations

The submitted residue data in conjunction with the data in EPA files are adequate to establish a permanent tolerance for avermectin in or on bell peppers. TOX considerations permitting, CBTS recommends a tolerance of 0.01 ppm avermectin in/on bell peppers. A DRES run may be initiated at this time.

Detailed Considerations

Manufacture and Formulation

The manufacturing process of technical grade avermectin has been adequately described (memo, L. Cheng, 5/1/86). No further data is required for this petition.

Proposed Use

Deficiency: Comment 1; Paragraph #2 (PP#3F4258, 6/21/94)

"The maximum application rate must be clearly stated on the proposed draft label and Section G. Currently, each section states a different maximum application rate. Revised Sections B and G should be submitted to resolve this discrepancy."

Registrant's Response:

"We agree that revised Sections B and G are needed..." Revised Sections B and G are included in the response.

CBTS Comments and Conclusions

The proposed use directions, Section B, are adequate. The product is applied at a rate of 0.01-0.02 lb (8 - 16 fl oz) ai/A using a

minimum of 20 gal of water per acre. Apply thoroughly as a foliar spray to assure good upper and lower leaf coverage. The product is applied when pests are first observed and application repeated at no less than 7 day intervals. No more than two sequential applications are made in order to manage the onset of resistance. The product may be applied to a maximum of 0.06 lb (48 fl oz) ai/A. The PHI after last application is 7 days. Aerial application equipment is not used with this product.

Nature of the Residue-Plants

Plant metabolism studies were not submitted with this petition. However, metabolism studies on citrus, celery, and cotton have been reviewed in conjunction with PP#s 5G3220, 5G3287, and 8F3649 and summarized in conjunction with PP#9F3703, 12/15/89. The available metabolism data is sufficient and the nature of the residue on fruiting vegetables is understood (PP#3F4258, 6/21/94). The residues of concern are avermectin B_1 and the delta-8,9-isomer. No further data are necessary for this proposed use.

Nature of the Residue-Animals

Animal metabolism studies were not submitted with this data package. However, avermectin metabolism in goat and rat has been reviewed. The residues of concern in animals were determined to be avermectin B_1 and the delta-8,9-isomer based on a feeding level of 1.0 mg/goat/day of ^{3}H-avermectin. New animal metabolism studies using ^{14}C-avermectin would be needed if the expected dietary burden exceeded the dose level in the goat metabolism study (PP#8F3592/8H5550, 6/21/89 and PP#1F3973/1H5611, 11/26/91). The residues of concern in animals remain avermectin B_1 and the delta-8,9-isomer. No further data is required for this proposed use.

Analytical Method-Enforcement MRID#433346-00

Adequate enforcement methods are available for avermectin in PAM II for citrus and processed fractions (Method I), ginned cottonseed (Method IA), and bovine tissues and milk (Method II). A method tryout for avermectin in or on pears (Merck method #8000) was completed at the Analytical Chemistry Lab in Beltsville, MD (memo, J. Stokes, 4/16/92). The method used here was Merck Method #8004, essentially method #8000 revision 4. The method has been forwarded to FDA to be published in PAM II (PP#1F3787, 12/16/93).

In Merck Method #8004 samples are treated with pectinase and then residues of avermectin extracted with acetonitrile/water. The extract is filtered then passed through a C8 column; the eluant is discarded and the avermectins eluted with acetonitrile. The acetonitrile is concentrated, water added, and the aqueous acetonitrile is extracted with hexane. The hexane extracts are loaded onto an aminopropyl column, the hexane eluant discarded, the

column washed with hexane, toluene, and methylene chloride, and the avermectin eluted with 50:50 acetone/methylene chloride. The eluant is then evaporated to dryness, and the residue dissolved and diluted to 10 mL in methylene chloride. The sample is split and evaporated to dryness, then derivatized with N,N-dimethylformamide, trifluoroacetic anhydride, and 1-methylimidazole followed by reaction with methanolic ammonium hydroxide. Derivatized residue is then separated from the reagents on a silica gel column, the eluant is dried and dissolved in methanol. The derivatization allows for reversed-phase HPLC with fluorescence detection. The limit of quantitation (LOQ) for avermectin B_1a, the delta-8,9 isomer and for avermectin B_1b is 5 ppb. The limit of detection (LOD) for the residues of interest was reported as 2 ppb.

Fortifications were made only with avermectin B_1a. The instrument was calibrated only with avermectin B_1a. The method has been validated for both forms of avermectin B_1 and the delta-8,9 isomer. Although not strictly correct analytical procedure, Merck has previously provided sufficient data showing the accuracy of using the avermectin B_1a calibration curve to quantitate avermectin B_1b (PP#3F4258, 6/21/94). Recoveries of avermectin B_1a from bell peppers submitted here ranged from 71-92% for fortifications from 5-50 ppb. Sample chromatograms and calibration curves were included in the submission.

Analytical Method-Multiresidue MRID#433346-00

Avermectin is not recovered with protocol A in PAM I. Other multi-residue protocols are not applicable to avermectin (ID#284941, review of 11/2/93). This is not a deficiency for this petition.

Magnitude of Residue MRID#433346-00

Deficiency: Comment 2; Paragraph #8b (PP#3F4258, 6/21/94)

Due to "... questions raised by the petitioner as to the quantity of active ingredient present in the formulation at the time of the pepper field trials (Nos. 001-90-1014R (NM), 001-90-1013R (CA), and 001-90-6011 (CA)), the petitioner may need to repeat the three field trials in question."

Registrant's Response:

"These three bell pepper field residue trials have been repeated and are included as Document No. 2 of this submission..."

CBTS Comments and Conclusions

The data from three studies were submitted here. Two studies were conducted in California (001-92-6008R, 001-92-6009R) and one in New

Mexico (001-92-1015R). These studies replaced the three studies submitted earlier which had questionable ai levels (PP#3F4258, 6/21/94). All three studies were conducted in the following manner: four applications at the maximum application rate, 0.02 lb ai/A, at seven day intervals for a total of 0.08 lb ai/A or 1.3 x maximum use rate. Samples for these studies were collected after the last application on day 0, then on day 3 and day 7. The combined residues of avermectin B_1a and the delta-8,9-isomer for all the samples ranged from ND (no detect < 2 ppb) to 31.8 ppb, found on a day 0 sample from one of the California studies, 001-92-6008R. The residues of avermectin B_1b for all the samples ranged from ND to NQ (less than 5 ppb but greater than 2 ppb). The highest residue found for the PHI, 7 days, was 7.5 ppb for the combined residues of avermectin B_1a and the delta-8,9-isomer. Recoveries of fresh avermectin B_1a fortifications of 5-50 ppb ranged from 71-92%.

Merck has indicated in their previous report that the data from three field trials (CA 001-90-1013R, NM 001-90-1014R, and CA 001-90-6011R) were compromised since the percentage of active ingredient at the time of applications could not be confirmed (PP#3F4258, 6/21/94). The remaining field trials submitted were conducted in Florida, Pennsylvania, South Carolina, and Texas (2). Together with the data the submitted here, the eight acceptable studies adequately represent the geographical distribution of the bell pepper growing regions in the U.S.

The two field trials in TX were conducted at application rates of 1 x (0.02 lb. ai/A) and 2 x (0.04 lb. ai/A). All other trials were conducted at the 1 x rate. Avermectin was applied at approximately 7 day intervals with 5-11 applications per trial. Samples were collected on the day of the last application (day 0), and at 3 days. Total avermectin residues, avermectin B_1a, the delta-8,9 isomer and avermectin B_1b, for the 3 day samples ranged from ND to NQ. The total avermectin residue for a 7 day sample detected in one of the field trials which may or may not be valid, CA 001-90-6011R, was at NQ (PP#3F4258, 6/21/94).

Deficiency: Comment 3; Paragraph #8c&d (PP#3F4258, 6/21/94)

"8c. CBTS cannot determine whether the proposed tolerance of 0.01 in or on the fruiting vegetable crop grouping is adequate. The petitioner needs to submit additional residue data for a variety of peppers which is smaller than the bell pepper. At least three additional field trials would be necessary. These three field trials could replace the three trials of which Merck has raised concerns. Two of the three would need to be conducted in CA if they were intended to replace the three trials in question. At least one non-bell pepper trial is required in New Mexico.

8d. CBTS could consider a petition for a tolerance for bell peppers based on the data submitted in conjunction with this petition for

the crop group tolerance. The petitioner would need to submit a revised Section F which proposes a tolerance for peppers, bell at 0.01 ppm and address all remaining deficiencies cited in this review. The petitioner would be requesting the tolerance for bell peppers in lieu of the crop group tolerance."

Registrant's Response:

"Currently , four abamectin-chili pepper residue trials are being conducted in the United States, one each in California, Arizona, New Mexico, and Texas. As these trials are still ongoing, we are submitting a revised Section F as indicated in the comment above, to propose a tolerance for abamectin on the bell peppers only, until the chili pepper data are available in early 1995.

CBTS Comments and Conclusions

The data presented here in conjunction with previously presented data are sufficient to establish a tolerance of 0.01 ppm for abamectin on bell peppers. A fruiting vegetable group tolerance for abamectin will be considered upon receipt of the chili pepper data.

Storage Stability

Storage stability studies were not submitted in conjunction with this petition. Bell pepper samples were frozen the same day as harvest and remained frozen until analysis. Samples were stored from 2 to 5 months prior to analysis. Storage stability data are available in/on tomatoes for 19 months (PP#3F4258, 6/21/94), citrus for 12 months (PP#8F3592, 6/21/89), and celery for 24 months (PP#8F3649, 5/4/90). There are adequate storage stability data to support the residue data of avermectin on bell peppers. No further data are required for this proposed use.

Meat, Milk, Poultry, and Eggs

There are no feedstock uses for bell peppers. No feedstock residue data were submitted or are necessary for this proposed use.

Deficiency: Comment 4, Paragraph #10

"...the petitioner should submit a revised section F proposing the 0.015 ppm tolerance on fat, cattle."

Registrant's Response:

" A revised Section F for Pesticide Petition No. 1F3973/1H5611 (Abamectin In/On Tree Nuts) including a proposed tolerance for abamectin in cattle fat at 0.015 ppm was submitted 9/30/93 with Merck's responses... A copy of the revised Section F for this

Petition is provided for reference..."

CBTS Comments and Conclusions

No further action is necessary for this proposed use. However, the fat tolerance should be established.

Other Considerations

An International Residue Limit status sheet is attached to PP#3F4258, 6/21/94. Codex limits for the sum of avermectin B_1a, it's delta-8,9 isomer and avermectin B_1b have been established for sweet peppers at 0.02 ppm. No Canadian or Mexican limits have been established. For EPA to harmonize residues with Codex, the proposed tolerances would need to be increased to 0.02 ppm. The tolerance expression would not need to be changed. An increase in the tolerance for the purposes of harmonization would need to be based on toxicological considerations.

Acute and Chronic Exposure Assessment

Based on the procedures described in the review PP#9F3787, 12/21/94, the following assessments are made.

The pending tolerance for residues of avermectin on bell peppers is 0.01 ppm. No additional processed commodities are associated with this RAC. CBTS recommends that the proposed tolerance of 0.01 ppm be used as the acute anticipated residue for bell peppers.

Table I: Residues of Avermectin in/on Bell Peppers

Trial	State	Avermectin ppb B_1a	B_1b	Total
001-92-1015R	NM *	ND(1)	ND(0.25)	1.25
		ND(1)	ND(0.25)	1.25
001-92-6008R	CA *	ND(1)	ND(0.25)	1.25
		7.5	ND(1.88)	9.38
001-92-6009R	CA *	ND(1)	ND(0.25)	1.25
		NQ(5)	ND(1)	6.00
001-89-3001R	TX **	ND(1)	ND(0.25)	1.25
		ND(1)	ND(0.25)	1.25
		NQ(5)	ND(1)	6.00
		ND(1)	ND(0.25)	1.25
001-89-3002R	TX **	ND(1)	ND(0.25)	1.25
		ND(1)	ND(0.25)	1.25
		ND(1)	ND(0.25)	1.25
		ND(1)	ND(0.25)	1.25
001-90-0009R	FL **	NQ(5)	ND(1)	6.00
001-90-0027R	SC **	NQ(5)	ND(1)	6.00
001-90-3042R	PA **	ND(1)	ND(0.25)	1.25

ND = No Detect (<2 ppb)
NQ = No Quantitation (2-5 ppb)
* = 7 day PHI
** = 3 day PHI

From the data above, a mean of 2.85 ppb was determined (17 entries for a total of 48.38 ppb). CBTS recommends that a value of 0.002 ppm be used as the chronic anticipated residue for bell peppers.

Table II: Acute and Chronic Residue Values to be Used in the Dietary Risk Assessment of Avermectin

DRES Entry	Acute Risk ppm	Chronic Risk ppm
Peppers, bell	0.01	0.002

cc: RF, PP#3F4258, circ., Cutchin, SAB (Doyle)
7509C: CBTS, Reviewer (WDC), CM#2, Rm 804P, 305-5351, WDC:4/19/95
R/I: Sec. Head: R. Quick, 4/13/95; Br. Sr. Sci.: R. Loranger, 4/13/95; Br. Chief: E. Zager, 4/14/95